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ORIGINAL RESEARCH

Persistence of power Doppler ultrasonography-detected synovitis over 1 year of follow-up predicts poor prognosis in rheumatoid arthritis in clinical remission: the SONORE prospective longitudinal study

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ABSTRACT

Objectives (1) To assess the progression of ultrasonography-detected synovitis in a cohort of patients with rheumatoid arthritis (RA) in remission during 1 year of follow-up (2) to evaluate the ability of consecutive examinations of ultrasonography to predict relapse (R) or radiographic progression (RP) at 1 year.

Methods Patients with RA (2010 American College of Rheumatology-European Alliance of Associations for Rheumatology criteria) in clinical remission (Disease Activity Score in 28 joints (DAS28)<2.6 without clinically active synovitis) were included. An independent investigator performed ultrasonography every 3 months for 1 year. Ultrasonography-detected synovitis was defined as power Doppler-positive ultrasonography synovitis (PDUS) grade ≥1 in at least one joint. PDUS at ≥2 consecutive visits during the follow-up defined persistent PDUS. An increase of ≥1 point in the modified total Sharp score defined RP. An increase in DAS28-C-reactive protein (CRP)>0.6 or DAS28-CRP>3.2 and any modification of disease-modifying anti-rheumatic drugs or glucocorticoids defined relapse. Univariate and multivariate Cox regression analyses were used to evaluate factors associated with R/RP at 1 year.

Results PDUS was detected in 75 (65.2%), 66, 60, 46 and 29 of the 115 patients with RA at baseline and at months 3, 6, 9 and 12, respectively. 58 (50.4%) patients exhibited persistent PDUS. After 1 year, 22/85 (25.9%) experienced relapse and 12 (14.1%) showed RP. On multivariate analysis, factors predicting R/RP at 1 year were persistent PDUS (HR=2.98, p=0.014) and an increase in DAS28-CRP level at the visit before relapse (HR=4.36, p=0.004).

Conclusion Persistent PDUS during follow-up, rather than at baseline, predicted worse outcome at 1 year and requires careful monitoring.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Predicting outcomes in rheumatoid arthritis (RA) in clinical remission is crucial for optimising management.

WHAT THIS STUDY ADDS

⇒ Persistent power Doppler ultrasonography-detected synovitis predicted worse outcome in patients with RA in clinical remission earlier than did periodic clinical assessment alone.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Ultrasonography may be a valuable tool for assessing disease activity and predicting prognosis in RA even during periods of apparent clinical remission.

INTRODUCTION

Clinical remission is the current target for the management of rheumatoid arthritis (RA). European Alliance of Associations for Rheumatology (EULAR) recommendations highlight that the treatment target is to achieve and maintain remission or at least, minimal disease activity, with the goal of preventing structural damage progression and the development of disabilities. Clinical remission is defined as the absence of signs and symptoms of significant inflammatory activity.[1] Subclinical disease activity may persist in patients in clinical remission, and numerous studies demonstrated that MRI or ultrasonography can frequently detect synovitis in RA even in the presence of clinical remission[2–5] whatever the definition of clinical remission used and a number of joints assessed for detecting subclinical inflammation.[6 7]

Ultrasonography has become an essential imaging modality in the management of RA

and is widely used as a clinical tool in routine care in rheumatology. This technique is effective for early diagnosis of inflammatory arthritis, predicting the development of RA in individuals at risk and assessing disease activity, structural damage, response to treatment and clinical remission. Its numerous advantages have been highlighted in the EULAR recommendations for using imaging for the clinical management of RA.[8]

A meta-analysis of longitudinal studies showed that at least one persistent power Doppler (PD)-positive ultrasonography synovitis (PDUS) grade ≥1 predicted clinical relapse and radiographic progression in individuals, over 1–2 years,[6] which demonstrates that subclinical synovitis represents incomplete suppression of inflammation. Consequently, whether only clinical composite scores can be used as a treatment target in clinical practice is an issue. In such settings, consideration should be given to the disease duration (ultrasonography-detected synovitis is more prevalent in established than early RA[9]); the joint location (particularly if concomitant osteoarthritic lesions are present) and the joint damage.

Ultrasonography is able to detect residual inflammatory lesions; however, the longitudinal relation between clinical remission and repeated ultrasonography-detected residual lesions during follow-up is not well known. In particular, the current understanding is limited regarding whether persistent subclinical synovitis in patients undergoing stable treatment will eventually resolve over time or if it may contribute to further joint damage and poor outcomes.

The primary objectives of the current study were to determine the prevalence of PDUS in a cohort of patients with RA in clinical remission and to investigate the progression of synovitis during follow-up. Secondarily, we aimed to assess the ability of baseline and consecutive ultrasonography detecting synovitis to predict unfavourable outcomes, such as clinical relapse or radiographic progression, within a 1-year time frame.

METHODS

The SONORE study is a longitudinal prospective study (ClinicalTrials.gov: NCT02618954) conducted in the rheumatology department of Montpellier University Hospital, France, from September 2013 to September 2016. Written informed consent was obtained from all patients, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Patients

Patients were eligible if they were ≥18 years old, fulfilled the 2010 American College of Rheumatology (ACR)-EULAR classification criteria for RA,[10] were receiving stable treatment with conventional synthetic and/or biological (b) disease-modifying anti-rheumatic drugs (DMARDs) and had been in clinical remission for less than 6 months, defined by a Disease Activity Score in 28 joints-erythrocyte sedimentation rate (DAS28-ESR)<2.6 and absence of clinically active synovitis (ie, no swollen and tender joint). Exclusion criteria were treatment with rituximab, unstable dosing regimen of corticosteroids within 1 month before study entry or doses of prednisone >5 mg per day or intra-articular injection within 2 months before baseline. Treatment, including glucocorticoids, had to remain unchanged (no tapering strategy) throughout the study period unless patients experienced a disease flare or safety concerns arose.

Baseline assessment

Demographic, socioeconomic data, disease history and biological features of arthritis, as well as past and current treatments, were collected at baseline. The date of clinical remission was recorded. Two independent investigators performed physical examinations every 3 months over 1 year to assess RA disease activity, including morning stiffness, joint pain at night, patient global assessment on a 100 mm Visual Analogue Scale, tender joint count (TJC) and swollen joint count (SJC). Swelling and tenderness were defined according to standardised assessment recommendations from EULAR.[11] The reliability between the two investigators was excellent, with very good agreement by the intraclass correlation coefficient: 0.79 (95% CI 0.61 to 0.89, p<0.001) for TJC and 0.96 (95% CI 0.92 to 0.98, p<0.001) for SJC. Clinical evaluators were blinded to ultrasound data during all visits.

Blood tests for C reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), rheumatoid factor and anti-CCP2 antibodies were performed at baseline. CRP measurement was repeated, and DAS28-CRP was calculated every 3 months for 1 year or until relapse. At each visit, the clinical investigator, who was aware of all clinical and biological results, determined whether the patient had persistent remission or relapse. Treatment with DMARDs and glucocorticoids (GCs) was recorded at each visit. Patients who were considered in clinical relapse discontinued the study.

Radiographic evaluation

Radiographs of the hands, wrists and feet were obtained at baseline and 1 year and were scored using the modified total Sharp score[12] by an experienced rheumatologist and blinded to other patients' data.

Ultrasonography examination

A MyLab 70 ultrasonography machine (Esaote, Genova, Italy) with a 12–18 MHz linear array transducer was used for all examinations. During PD evaluation, the Doppler frequency was set at 9.1 MHz, the pulse repetition frequency at 750 Hz and the Doppler gain just below the noise level. PD settings for slow flow were kept unchanged throughout the study. The size and position of the colour box were set at the top of the image to recognise artefacts caused by vessels above the joint. Grey-scale and PD ultrasonography were performed for 40 joints including the

shoulder, elbow, wrist (radiocarpal, midcarpal, distal radioulnar joint, the highest score used as representative for the wrist), metacarpophalangeal joints 1–5, interphalangeal joints, knee, ankle and metatarsophalangeal joints 1–5, bilaterally for the presence of synovial hypertrophy and PD signal at baseline and every 3 months for 1 year or until relapse. The presence of synovitis (ie, synovial hypertrophy with or without PD signal) was scored according to the Outcome MEasures in Rheumatoid Arthritis Clinical Trials (OMERACT)–EULAR synovitis composite scoring system with a semiquantitative scale (0–3) separately and in combination, at the joint and the patient level by using the Global OMERACT-EULAR combined Synovitis Score (GLOESS).[13 14] Ultrasonography-detected synovitis was defined as PDUS grade ≥1 in at least one joint. Persistence of PDUS was defined by the presence of synovitis in the same joint in at least two consecutive visits, excluding the visit of relapse from this definition, to investigate whether ultrasonography can predict a flare in the visit before relapse. At the patient level, we calculated the number of synovitis with PD grade ≥1 or ≥2 among 40 joints. Ultrasonography examinations were performed by a sonographer with extensive experience in musculoskeletal ultrasonography, trained in the OMERACT-EULAR synovitis scoring system and with masking to clinical and radiographic data. During the examination, the room was dark, the sonographer never inspected the patient and was not allowed to talk with him. The sonographer was not involved in clinical decision-making during the study, and the examination time per patient was approximately 20 min.

Outcome measures

The primary outcome, referred to as the 'unfavorable outcome', was defined as the presence of radiographic progression from baseline to 1 year, defined by an increase of at least one point in the modified total Sharp score or a relapse observed at any of the visits during the study period, defined by an increase in DAS28-CRP>0.6 between two visits or a DAS28-CRP>3.2 at one or more follow-up visits, accompanied by any modification of DMARDs due to insufficient efficacy or GC administration (>5 mg/day for ≥15 days) including intra-articular injection if >1 injection was given.

To compare the predictive ability of clinical examination and ultrasonography for predicting relapse at the next visit, we created a supplementary variable called 'disease activity worsening'. This variable was defined as DAS28-CRP>3.2 at the visit before relapse, accompanied by a change in DAS28-CRP>0.6 between this visit and the previous one (ie, between 6 and 3 months before relapse), without any change in treatment. In the same way, 'ultrasonography worsening' was defined by PDUS grade ≥1 in at least one joint at the visit before relapse.

Sample size calculation

Previous data suggested an approximately 50% prevalence of clinical relapse or radiographic progression in patients with RA in remission or with low disease activity.[6] Using a sensitivity and specificity of 80% each and bilateral accuracy of 12%, we estimated the sample size at 86 patients. Taking into account potential missing data and patients lost to follow-up, estimated at 25%, we planned to include 108 patients.

Statistical analysis

Demographic characteristics and baseline disease activity measures are reported as mean (SD), or number (%) as appropriate. The normality of distribution for quantitative variables was assessed with Shapiro-Wilk tests. Survival analysis involved using Kaplan-Meier curves to evaluate the association between baseline PDUS, persistent PDUS and risk of poor outcome (defined as clinical relapse or radiographic progression) during follow-up. Baseline variables, including PDUS and its persistence during the follow-up, were assessed for their association with time and progression to unfavourable outcome by univariate Cox analysis to obtain HRs and their 95% CIs. Explanatory variables with p<0.20 on univariate analysis were included in the multivariate Cox regression model. A stepwise procedure was used to determine relevant independent baseline variables predicting poor outcome at 1 year in the multivariate analyses. Significance was defined as p<0.05 for variables included in the multivariate model. Analysis involved using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient characteristics

The baseline characteristics of the 115 patients with RA included in the study are summarised in table 1. The mean (SD) symptom duration was 9.3 (±9.3) years, and the duration of clinical remission 2.1 (±2.3) months. The mean (SD) DAS28-CRP was 1.89 (±0.51). Only 23 (20%) patients fulfilled ACR/EULAR remission criteria. 57 (51.4%) presented radiographic erosions.

Among the 115 patients, 3 were lost to follow-up, 2 had a serious adverse event, 1 had an exclusion criterion and 24 refused to participate in the entire study, which resulted in 85 evaluable patients at 1 year. Of note, 16 patients had missing data for one visit during follow-up, but they had available data at 1 year and they were maintained in the main population of analysis (figure 1).

At 1 year, among the 85 patients with available data, 63 (74.1%) were still in clinical remission and for 22 (25.9%) disease had relapsed (2 at month 3, 6 at month 6, 11 at month 9, 3 at month 12), 12 (14.1%) had radiographic progression and 28 (32.9%) an unfavourable outcome (relapse or radiographic progression; 6 patients had both) (table 1).

Ultrasonography-detected synovitis

At baseline, 75 of 115 patients (65.2%) had PDUS grade ≥1 detected in at least one joint. Among patients with PDUS, most had 1, 2 or 3 synovitis location with PDUS grade ≥1, as shown in table 2.

Table 1 Demographic and baseline characteristics of the patients with rheumatoid arthritis (n=115)

	Overall population		Relapse or radiographic progression				P value*
		N	No	N	Yes	N	
Female, n (%)	86 (74.8)	115	63 (72.4)	87	23 (82.1)	28	0.30
Age (years), mean (SD)	58.9 (±12.8)	115	58.3 (±13.4)	87	60.5 (±10.4)	28	0.43
Disease duration (years), mean (SD)	9.3 (±9.3)	114	8.4 (± 9.4)	86	12.3 (±8.6)	28	<0.01
Duration of clinical remission (months), mean (SD)	2.1 (±2.3)	106	2.2 (±2.4)	80	1.9 (±2)	26	0.57
Body mass index (kg/m^2), mean (SD)	25.3 (±5.1)	111	25.7 (±5.4)	85	24.1 (±4)	26	0.25
Tender joint count/28 joints, mean (SD)	0.47 (±1.07)	115	0.37 (±0.97)	87	0.79 (±1.32)	28	0.01
Swollen joint count/28 joints, mean (SD)	0.31 (±0.75)	115	0.26 (±0.69)	87	0.46 (±0.92)	28	0.16
Patient global assessment (0–100), mean (SD)	18.8 (14.6)	115	18.9 (±14.7)	87	16.8 (±12.1)	28	0.56
Anti-CCP antibody-positive, n (%)	91 (79.1)	115	67 (77.0)	87	24 (85.7)	28	0.32
Rheumatoid factor-positive, n (%)	86 (75.4)	114	62 (72.1)	86	24 (85.7)	28	0.15
ESR (mm/h), mean (SD)	13.5 (±9.8)	46	12.7 (±8.8)	33	15.8 (±12.2)	13	0.55
CRP (mg/L), mean (SD)	4.3 (±6.7)	114	4.7 (±7.4)	86	2.8 (±3.3)	28	0.18
DAS28-ESR, mean (SD)	2.03 (±0.63)	46	1.92 (± 0.65)	33	2.30 (±0.53)	13	0.07
DAS28-CRP, mean (SD)	1.89 (±0.51)	114	1.87 (±0.50)	86	1.95 (±0.56)	28	0.46
Fulfilled ACR/EULAR remission criteria, n (%)	23 (20)	115	19 (21.8)	87	4 (14.3)	28	0.38
Current smoking, n (%)	24 (21.2)	113	18 (20.9)	86	6 (22.2)	27	0.27
Radiographic erosions, n (%)	57 (51.4)	111	40 (47.6)	84	17 (63.0)	27	0.17
Current csDMARD, n (%)	92 (80)	115	71 (81.6)	87	21 (75)	28	0.44
Current bDMARD, n (%)	74 (64.4)	115	55 (63.2)	87	19 (67.9)	28	0.66
Glucocorticoids, n (%)	31 (27)	115	22 (25.3)	87	9 (32.1)	28	0.48

*X^2, Student's or Wilcoxon-Mann-Whitney test as appropriate.
ACR, American College of Rheumatology; bDMARD, biological disease modifying anti-rheumatic drug; CRP, C-reactive protein; csDMARD, conventional disease-modifying antirheumatic drug; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology.

During follow-up, 58 of 115 patients (50.4%) exhibited persistence of at least one PDUS grade ≥1 in the same joint for at least two consecutive visits. The mean (SD) time before elimination of PDUS grade ≥1 was 5.34 (±2.70) months. Similarly, at baseline, 42 of 115 patients (36.5%) had PDUS grade ≥2 in at least one joint. Most of these patients had one synovitis location with PDUS grade ≥2. During follow-up, 26 of 115 patients (22.6%) exhibited persistence of at least one PDUS grade ≥2 in the same joint for at least two consecutive visits. The mean (SD) time before elimination of PDUS grade ≥2 was 5.27 (±2.74) months.

Progression of PDUS during follow-up

Overall, 66/106 patients (62.9%) at month 3, 60/96 patients (61.9%) at month 6, 46/94 patients (49.5%) at month 9 and 29/85 patients (34.1%) at month 12 had PDUS grade ≥1 in at least one joint. Similarly, 28 of 106 patients (26.7%) at month 3, 30 of 96 (30.9%) at month 6, 17 of 94 (18.3%) at month 9 and 18 of 85 (21.2%) at month 12 had PDUS grade ≥2 in at least one joint. In contrast, the mean DAS28-CRP remained stable during follow-up (data not shown).

Factors associated with relapse or radiographic progression at 1 year: univariate analysis

After 1 year of follow-up, 28/85 (32.9%) experienced an unfavourable outcome at 1 year: 22/85 (25.9%) relapses (2 patients at month 3, 6 at month 6, 11 at month 9 and 3 at month 12), and 12 (14.1%) radiographic progression. Six patients experienced both radiographic progression and relapse. On univariate analysis, unfavourable outcome was associated with baseline TJC and several variables at the visit before relapse: SJC, TJC, DAS28-CRP>3.2 with change in DAS>0.6 and presence of at least one PDUS (table 3). The unfavourable outcome was also associated with the persistence of at least one PDUS (HR=2.44, 95% CI 1.08 to 5.55, p=0.033). In contrast, PDUS at baseline was not significantly associated with an unfavourable outcome at 1 year (p=0.201).

Predictors of relapse or radiographic progression at 1 year

Factors associated with multivariate analysis with relapse or radiographic progression at 1 year are shown in table 4. Independent predictors of unfavourable outcome at 1 year were persistent PDUS (HR=2.98, 95% CI 1.24 to 7.16, p=0.014) and disease activity worsening (HR=4.36, 95% CI 1.62 to 11.78, p=0.004). Duration of remission, other baseline ultrasound findings including baseline

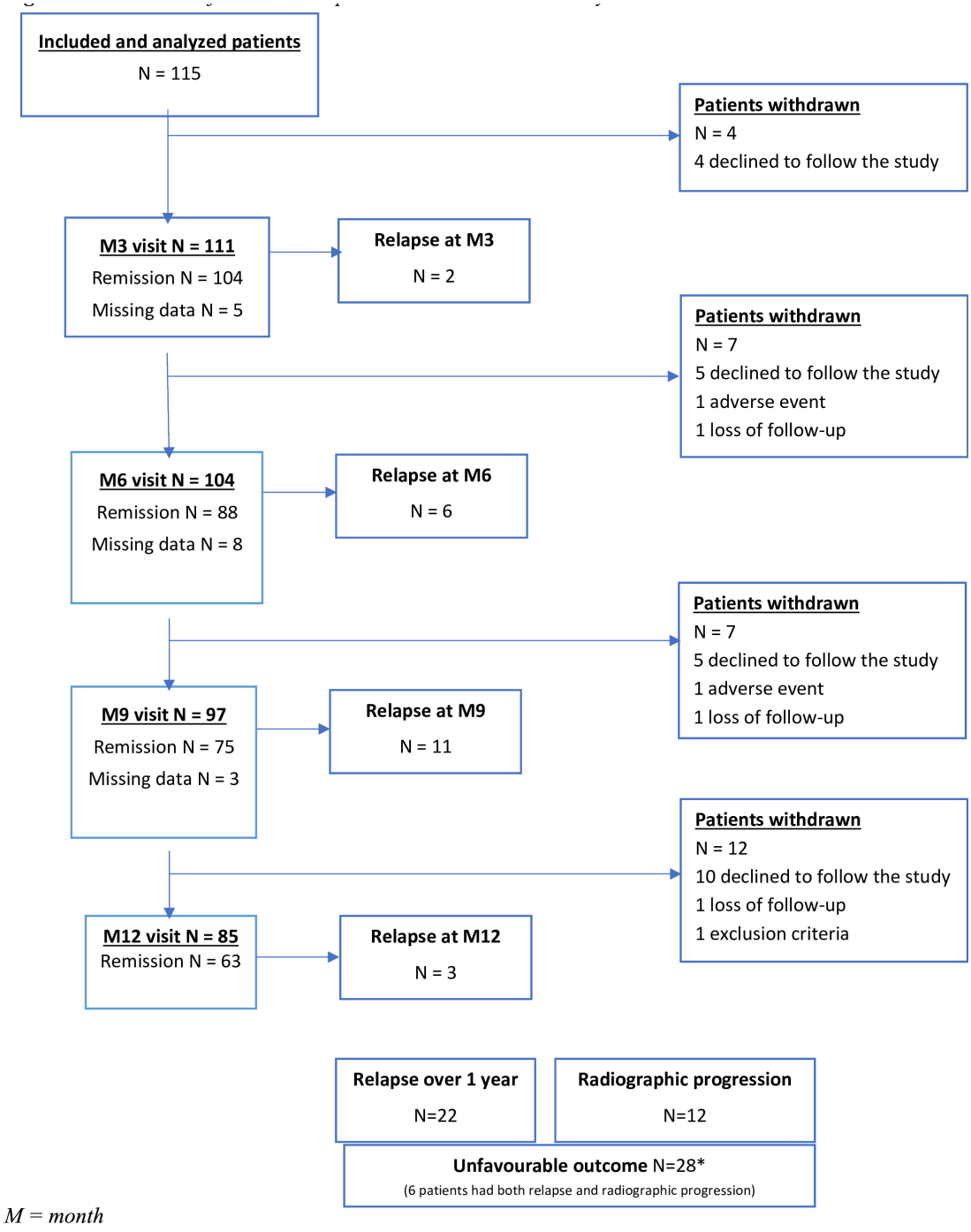

Figure 1 Flow chart of the included patients in the SONORE study.

PDUS, autoantibodies and erosive disease did not have additional predictive value in this model. To account for collinearity among variables such as DAS28 components (TJC, SJC, patient global assessment and CRP level), we selected the variable with the highest association in the multivariate model.

Secondary outcomes

On univariate analysis, clinical relapse was associated with baseline TJC and several variables at the visit before relapse: SJC, TJC, DAS28-CRP>3.2 with change in DAS>0.6 and presence of at least one PDUS at the visit before relapse (online supplemental table 1). No other ultrasonography variable was found associated with relapse during the 1-year follow-up. Clinical relapse was associated although not significantly with persistence of at least one PDUS grade ≥1 (HR=2.07, 95% CI 0.87 to 5.41, p=0.113). On multivariate analysis, independent predictors of clinical relapse at 1 year were disease activity worsening at the visit before relapse (HR=3.71, 95% CI 1.32 to 10.43, p=0.013) and PDUS synovitis at the visit before relapse (HR=3.16, 95% CI 1.13 to 8.82, p=0.028).

Table 2 Patients with at least one power Doppler ultrasonography synovitis (PDUS) grade ≥1 and ≥2 at baseline (n=115)

Number of PDUS locations	PDUS grade ≥1	PDUS grade ≥2
0	40 (34.8%)	73 (63.5%)
≥1	75 (65.2%)	42 (36.5%)
1	21 (18.3%)	24 (20.9%)
2	21 (18.3%)	7 (6.1%)
3	16 (13.9%)	5 (4.4%)
4	10 (8.7%)	4 (3.5%)
>4	7 (6.1%)	2 (1.7%)

On univariate analysis, radiographic progression at 1 year was associated with disease duration, baseline DAS28-ESR and persistent PDUS grade ≥1 (online supplemental table 2). Radiographic progression was also associated although not significantly with the presence of at least one PDUS at baseline (HR=7.33, 95% CI 0.91 to 59.28, p=0.062) and radiographic erosion at baseline (HR=2.99, 95% CI 0.74 to 12.04, p=0.123). At the joint level, PDUS grade ≥1 at baseline was associated with radiographic progression at 1 year (p<0.001). A similar conclusion can be drawn when ultrasonography synovitis was based on grey-scale synovial hypertrophy grade ≥2 (p<0.001). On multivariate analysis, the best predictor of radiographic progression was persistent PDUS grade ≥1 (HR=13.25, 95% CI 1.56 to 115.72, p=0.018). Disease duration was also a predictor (HR=1.08, 95% CI 1.00 to 1.14, p=0.037). Baseline PDUS, autoantibodies and erosive disease at baseline did not provide additional predictive value in this model.

DISCUSSION

We investigated the persistence of PDUS over 1 year of follow-up and its association with disease outcome. In total, half of the patients exhibited persistent PDUS. After 1 year of follow-up, 22 of 85 patients experienced relapse and 12 radiographic progression. Persistent PDUS synovitis more reliably predicted worse outcome in patients with RA in clinical remission than did periodic clinical assessment alone.

Most of the previously published longitudinal studies evaluating the predictive value of ultrasonography in RA in remission have typically involved a single ultrasonography examination at baseline to assess its association with later unfavourable outcomes. However, the SONORE study is a unique prospective longitudinal study that includes regular ultrasonography examinations to observe the evolution of ultrasonography-detected synovitis without interfering with the ongoing treatment. Our study population is representative of other cohorts of patients with RA in clinical remission.[15–18] The mean duration of clinical remission was less than 3 months, with the objective of following them for 1 year.

Table 3 Factors associated with relapse or radiographic progression at 1 year: univariate analysis

Variables	N	Univariate analysis HR (95% CI)	P value
Baseline variables			
Male vs female	115	0.60 (0.23 to 1.60)	0.311
Age	115	1.01 (0.98 to 1.04)	0.524
Disease duration	114	1.03 (1 to 1.07)	0.054
Duration of clinical remission	106	0.96 (0.81 to 1.14)	0.637
Current smoking (vs never)	113	0.90 (0.35 to 2.28)	0.821
Baseline TJC	115	1.37 (1.03 to 1.81)	**0.030**
Baseline SJC	115	1.25 (0.84 to 1.87)	0.278
Baseline ESR	46	1.01 (0.96 to 1.07)	0.594
Baseline CRP	114	0.93 (0.84 to 1.03)	0.151
Baseline DAS28-ESR	46	2.34 (0.85 to 6.43)	0.100
Baseline DAS28-CRP	114	1.32 (0.64 to 2.72)	0.460
Rheumatoid factor-positive	106	1.0 (0.99 to 1.0)	0.696
Anti-CCP antibody-positive	104	1.0 (0.99 to 1.0)	0.631
Radiographic erosion	111	1.67 (0.76 to 3.64)	0.200
At least one baseline PDUS	115	1.75 (0.74 to 4.11)	0.200
Variables during the follow-up			
AUC DAS28-CRP	104	0.96 (0.92 to 1.01)	0.124
At least one persistent PDUS	115	2.44 (1.08 to 5.55)	**0.032**
Variables at visit before relapse			
TJC at visit before relapse	111	1.12 (1.01 to 1.24)	**0.036**
SJC at visit before relapse	111	1.46 (1.14 to 1.87)	**0.003**
Patient global assessment at visit before relapse	106	1.02 (0.99 to 1.04)	0.145
CRP level at visit before relapse	104	0.98 (0.91 to 1.05)	0.533
DAS28-CRP>3.2 and delta DAS>0.6 at visit before relapse	104	3.61 (1.35 to 9.61)	**0.010**
DAS28-CRP at visit before relapse	104	1.63 (1.05 to 2.52)	**0.028**
At least one PDUS at visit before relapse	115	2.56 (1.16 to 5.66)	**0.021**

AUC, area under the receiver operating characteristic curve; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; PDUS, power Doppler ultrasonography synovitis; SJC, swollen joint count; TJC, tender joint count.

Therefore, the treatment was kept stable throughout the study period, ensuring sustained remission before tapering DMARDs. Nevertheless, the inclusion criteria were stringent and patients were not allowed to have both painful and swollen joints. Gartner *et al* demonstrated clinically active joints associated with higher grades of PD and grey-scale ultrasonography signals.[19] In our study, two-thirds of the patients had at least one joint with PD activity at baseline. This finding aligns with the results of a meta-analysis conducted by Nguyen *et al*, showing 44% prevalence of PDUS, regardless of the definition of clinical remission and the methods of ultrasonography

Table 4 Multivariate Cox regression analysis of predictors of relapse or radiographic progression at 1 year*

Variables	HR (95% CI)	P value
At least one persistent PDUS	2.98 (1.24 to 7.16)	0.014
DAS28-CRP>3.2 and delta DAS>0.6 at visit before relapse	4.36 (1.62 to 11.78)	0.004

The following were excluded from the model because of collinearity among variables: DAS28-CRP>3.2 at visit before relapse; DAS28-CRP at visit before relapse; TJC at visit before relapse; SJC at visit before relapse; patient global assessment at visit before relapse.
*Included variables: ≥1 PDUS at visit before relapse, ≥1 persistent PDUS, DAS28-CRP>3.2 and delta DAS>0.6 at visit before relapse, area under the receiver operating characteristic curve DAS28-CRP, disease duration, baseline TJC, baseline DAS28-ESR.
CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; PDUS, power Doppler ultrasonography synovitis; SJC, swollen joint count; TJC, tender joint count .

examination used (assessing 5–44 joints).[6] The cut-off of 1, which defines positive ultrasonography-detected synovitis by the OMERACT-EULAR synovitis composite scoring system using a semiquantitative scale of 0–3, is sometimes debated, because synovial hypertrophy with PD ultrasonography mostly at grade 1 has been reported in 9% of healthy subjects.[20] Even when considering PDUS grade ≥2, we still found that one-third of patients in clinical remission had at least one positive synovitis location.

To investigate the progression of PDUS, we conducted ultrasonography examinations every 3 months. Of note, the proportion of patients with at least one PDUS decreased over time, which suggests that clinical remission may precede ultrasonography remission. The presence of PDUS in clinically inactive joints may represent residual activity from previously observed clinical activity in the respective joint, which may resolve over time as clinical signs disappear and joint remission is maintained. Gartner *et al*[21] selected joints without clinical activity but showed ongoing sonographic signs of inflammation in 90 patients with RA with low disease activity or remission. The authors evaluated the time since the last clinical joint activity and found that the period of clinical remission was shorter for joints with high-grade than low-grade grey-scale signals (p<0.001). Results for PD signals were similar but not significant (p=0.069). However, the mean time since the last clinical swelling ranged from 2.2 to 4.5 years and was calculated retrospectively from medical records in this study.

The main objective of our study was to evaluate the predictive ability of PDUS in consecutive examinations for unfavourable outcomes. To increase the number of events, we chose a double outcome for our analysis. In most longitudinal studies in RA, clinical relapse and radiographic progression were considered as two outcomes associated with worse prognostic.[15 16 22] Accurate identification of patients at risk of clinical relapse and radiographic progression as well as those who may have sustained remission is crucial for successful tapering or discontinuation of bDMARDs. Although baseline PDUS was not used as a selection criterion, we found unfavourable outcome associated with persistent PDUS in at least two consecutive visits along with disease activity assessed by clinical evaluation at the visit before relapse. Of note, the clinical investigator, who determined persistent remission or relapse, had access to all clinical and biological results, but the ultrasonography assessments were independently conducted and blinded to the clinical investigator.

The persistence of PDUS may be present long before the clinical relapse and not necessarily limited to the visit before relapse. Only a few studies have evaluated ultrasonography findings in multiple examinations as predictors of outcome. In Macchioni *et al*,[23] which evaluated patients with early active RA, multiple factors predicted radiographic evidence of local erosions at 1 year, including baseline radiographic evidence of erosions, baseline grey-scale synovitis grade ≥2 and persistent PDUS grade ≥2 on two or more ultrasonography evaluations during follow-up. Therefore, persistent PDUS, along with other factors, may indicate an increased risk of radiographic evidence of erosions in patients with early active RA.

Two studies of early RA did not demonstrate the superiority of an ultrasonography tight control strategy, which targeted ultrasonography-detected remission, over a regular tight control strategy based on clinical evaluation in achieving clinical remission at 18 and 24 months.[24 25] In the TASER and ARTIC randomised controlled trials, patients with the ultrasonography tight control strategy more frequently were overtreated than the others, although not significantly, without significant improvement in clinical remission rate. In one of the studies, the ultrasonographer was aware of the clinical status of the patients.[24] Because of these differences among study designs, direct comparisons with our study are challenging. However, the ARTIC trial found a statistically significant reduction in radiographic progression in the ultrasonography tight-control strategy group, as measured by the change in modified total Sharp score (1 vs 1.5, p=0.05). The TASER trial showed reduced radiographic progression in the ultrasonography tight-control strategy group versus the others, although not significant, as measured by the change in modified Sharp erosion score (0 vs 0.5, p=0.07). Therefore, ultrasonography might be useful in determining the persistence of inflammation when structural damage is a major concern. Of note, in our study, we chose the persistence of PDUS predicting radiographic progression at 1 year in a secondary analysis.

We also observed the association of unfavourable outcome with disease activity as assessed by clinical evaluation at the visit before relapse. Results in the literature are conflicting regarding the association between clinical parameters and relapse in RA. In the Saleem *et al* study[22], PDUS synovitis and Health Assessment Questionnaire-Disability Index but not various clinical remission criteria predicted relapse at 12 months. In the study by Naredo *et al*,[18] the DAS28 before tapering predicted successful

tapering of medication. However, Terslev *et al*[7] did not find any clinical predictors explaining successful tapering or discontinuation, possibly because of the low residual disease activity in their cohort.

Our study has some limitations. First, the duration of clinical remission was relatively short, which may have allowed the inclusion of patients with clinical residual disease activity. Remission was defined as DAS28-ESR<2.6 and the absence of clinically active synovitis to include patients in remission according to the DAS, AND without any joint being concomitantly painful and swollen. The proportion of patients experiencing relapse during the 1-year follow-up was lower than anticipated for the sample size calculation. This observation may be partly due to the study design, which involved regular follow-up every 3 months and stable treatment during the entire follow-up period. The clinical investigator may have deferred treatment adjustment in case of uncertain relapse, which could have influenced the observed relapse rate. Another potential limitation is the strict definition of relapse, which required a change in DMARD therapy. This definition may have affected the observed relapse rate, because we could have excluded some patients who may have had milder disease activity or responded to other interventions without DMARD changes. Additionally, we did not include ultrasonography evaluation of tenosynovitis in our study, despite evidence from an Italian study suggesting that it may have additive predictive value in predicting relapse in patients with RA.[17]

The strengths of our study include the use of a homogeneous patient cohort, long follow-up and the study conducted in a routine care setting, which enhances its external validity. We used the OMERACT validated synovitis scoring system, including grey-scale, Doppler and GLOESS scoring, which allowed for a comprehensive assessment of ultrasonography findings in multiple joints. Moreover, we followed patients prospectively at regular intervals of 3 months for 1 year, which allowed for a thorough evaluation of disease activity and relapse. These strengths contribute to the robustness and reliability of our findings and provide valuable insights into the association between ultrasonography findings and relapse in patients with RA.

In conclusion, our results indicate that residual PDUS was detected at baseline in a substantial proportion of patients with RA in clinical remission and is not necessarily associated with a poor outcome in our cohort. However, persistent PDUS during follow-up rather than baseline PDUS was a significant predictor of unfavourable outcome at 1 year in patients with RA in clinical remission. Hence, initial ultrasound findings may not be sufficient to justify a therapeutic change. However, the persistence of residual PDUS requires careful follow-up and might even merit strategy adaptation.

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